

Calcinosis in Rheumatic Diseases

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BACKGROUND Calcinosis, or dystrophic soft-tissue calcification, occurs in damaged or devitalized tissues in the presence of normal calcium/phosphorus metabolism. It is often noted in the subcutaneous tissues of connective tissue diseases—primarily systemic lupus erythematosus, scleroderma, or dermatomyositis—and may involve a relatively localized area or be widespread. The calcinotic accumulations may lead secondarily to muscle atrophy, joint contractures, and skin ulceration complicated by recurrent episodes of local inflammation and infection.

OBJECTIVES To review the classification, pathogenesis, clinical features, and treatment of calcinosis in rheumatic diseases.

METHOD A MEDLINE search of articles from 1972 to 2004 was conducted utilizing the index word “calcinosis” with the coindexing terms “scleroderma,” “lupus,” “dermatomyositis,” and “dystrophic calcification.”

RESULTS Calcinosis may be the source of both pain and disability in connective tissue disease patients. Illustrative cases of patients with severe calcinosis are described. The literature available was critically reviewed. While warfarin, colchicine, probenecid, bisphosphonates, diltiazem, minocycline, aluminum hydroxide, salicylate, surgical extirpation, and carbon dioxide laser therapies have been used, no treatment has convincingly prevented or reduced calcinosis.

CONCLUSIONS Calcinosis is common in the conditions reviewed and a number of agents have been used for treatment. However, the approach to calcinosis management is disorganized, beginning with the lack of a generally accepted classification and continuing with a lack of systematic study and clinical therapeutic trials.

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Calcinosis, or nonarticular soft-tissue calcification, is a not infrequent accompaniment of rheumatic disease, which occurs in tissues altered by structural damage, hypovascularity, or tissue hypoxia. Calcinosis may involve a relatively localized area or it may be widespread, causing secondary muscle atrophy, joint contractures, and skin ulceration, with recurrent episodes of local inflammation or infection and debilitating complications. We report 2 illustrative patients with rheumatic diseases and calcinosis that we recently

encountered in our hospital and review the subject systematically, including the classification, pathogenesis, clinical features, and treatment. A detailed description of calcinosis in genetic and vascular disease, which embodies a vast literature, is beyond the scope of this article.

Case 1

An 80-year-old woman, who had been diagnosed with the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) variant of scleroderma (SSc), hypertension, recurrent gastric bleeding due to “watermelon stomach,” and mild dementia, was hospitalized with prolonged fever and deterioration in general function. Physical examination was notable for hard cutaneous plaques overlying both hips, shoulders, elbows, wrists, and fingers, with small areas of skin ulceration. The joint examination revealed swelling, tenderness, warmth, and erythema at the

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Figure 1 Calcifications in the shoulder region.

right elbow with widespread ulceration of hard cutaneous calcified plaques over the extensor joint surface. The shoulders were severely limited in range of motion. No respiratory, urinary, meningeal, or other source for the fever could be determined. Laboratory values were largely unremarkable, with serum calcium and phosphorus within normal limits, antinuclear antibody (ANA) positive, and extractable nuclear antigen (ENA) screen negative. Radiographs (Fig. 1) demonstrated remarkable cutaneous and subcutaneous calcifications about most joints, most notably shoulders and elbows. She was treated with nonsteroidal antiinflammatory drugs (NSAIDs) and ceftriaxone and the fever resolved. Calcium deposits that were secondarily infected were felt to be the cause of her febrile illness. Her reduced function and disability were attributed to muscle atrophy and joint contractures also secondary to calcinosis. A brief trial of diltiazem resulted in hypotension and altered mentation. On the basis of her age and comorbidities, only conservative local wound care was provided.

Case 2

A 20-year-old woman with a history of systemic lupus erythematosus (SLE) since age 18 presented with increased oral ulcers, arthralgias, fatigue, "butterfly" facial rash, and erythematous plaques on her skin. Her physical examination revealed, additionally, finger cyanosis of Raynaud's phenomenon, arthritis of the wrists, and sclerotic erythematous cutaneous plaques resulting in disfigurement of the upper arms and contractures of the elbows. Skin biopsy demonstrated lobular and septal panniculitis. Blood chemistries were unremarkable, with serum calcium and phosphorus within normal limits. Serology findings were significant for a positive ANA and anticardiolipin antibodies. Technetium bone scan (Fig. 2) was notable for linear subcutaneous uptake of the isotope in the proximal extremities with roentgenograms showing fine calcific subcutaneous deposits along the humeri and femurs. She was treated for lupus panniculitis with calcinosis with colchicine, prednisone, hydroxychloroquine,

and azathioprine with gradual lessening of induration of the skin lesions, reduction in their size, and improved elbow range of motion.

Methods

A MEDLINE search of articles from 1972 to 2004 was conducted utilizing the index word "calcinosis" with the coindexing terms "scleroderma," "lupus," "dermatomyositis," and "dystrophic calcification." References noted in relevant articles also were accessed. The articles reviewed herein are not exhaustive, with preference given, where possible, to series over individual case reports.

Classification of Soft-Tissue Calcification

Calcification of the soft tissues may represent a nonspecific local response or be a manifestation of a complex underlying disease. A unitary, generally accepted, classification of calcification is not to be found in the literature (1-8), some feeling that the division should simply be between idiopathic or metabolic disorders. In 1975 Greenfeld (1) first described 3 types of soft-tissue calcification: metastatic calcification (some feel this term is best reserved for cancer); generalized calcinosis, which included calcification in collagen vascular disorders, idiopathic tumoral calcinosis, and idiopathic calcinosis universalis; and dystrophic calcification. Black and Kanat (2) in 1985 also classified soft-tissue calcifications into 3 similar categories: metastatic calcification, dystrophic calcification, and calcinosis. Later, Marzano and coworkers (3) expanded soft-tissue calcification into 4 somewhat different clinical types: dystrophic, including calcinosis in this group; idiopathic; tumoral; and metastatic. In 2002 Wilmer and coworkers (4) proposed an additional type of soft-tissue calcification, namely, calciphylaxis (the presence of a "calcifer," eg, parathyroid hormone (PTH) or vitamin D, is at variance with calcinosis). In consideration of the above representative



Figure 2 Bone scan. Subcutaneous calcifications of both arms.

literature, the following may be considered the current comprehensive classification of soft-tissue calcifications: metastatic, tumoral, idiopathic, dystrophic calcification—which includes calcinosis (1,2,3,8), and calciphylaxis (4):

(a) “Metastatic” calcification is associated with abnormal serum calcium-phosphorous levels and involves normal tissues. It is associated with diseases such as hyperparathyroidism, malignancies, milk-alkali syndrome, or hypervitaminosis D. (2) The condition most commonly affects the media of arteries and visceral organs, but is also found occasionally as firm nodules located in subcutaneous tissues in the vicinity of large joints (3).

(b) Tumoral calcification is a rare familial disorder found in patients with an elevated serum phosphorus level but normal calcium level and usually presents with large subcutaneous calcium deposits near joints or pressure areas (5,6).

(c) Dystrophic calcification, which includes calcinosis, occurs in the presence of normal metabolism and takes place in presumably damaged or devitalized tissues. It is noted most often in subcutaneous tissues secondary to trauma or infection and also is described in SLE, scleroderma, or dermatomyositis (DM) (3). It is generally found as an incidental radiologic finding, exhibiting a predilection for the extremities and buttocks. Clinically, it may present as subcutaneous nodules or plaques or extensive small or large cutaneous deposits. Serum calcium and phosphorus values are normal.

(d) Idiopathic calcification occurs in otherwise healthy persons with normal metabolism. Multiple, asymptomatic subcutaneous nodules appear in childhood or in early adult life and may be localized or generalized (7).

(e) Calciophylaxis is that calcification which predominates in individuals with chronic renal failure and abnormal calcium-phosphorous levels. Small vessel vasculopathy with mural calcification and intimal proliferation, fibrosis, and thrombosis occurs (4), with secondary ischemia and necrosis of tissues.

Pathogenesis (Fig. 3)

Although normal physiologic tissue concentrations of calcium (Ca) and phosphate (P) are close to their saturation, tissue calcification is unusual due to the presence of endogenous inhibitors of calcification (9). Dystrophic calcification occurs in tissues that have been altered in some way to promote calcification, but with normal serum levels of Ca and P. Pathophysiologic changes that promote calcification may include tissue structural damage, hypovascularity and hypoxia, age-related tissue changes, and genetically determined predispositions favoring calcification. Calcification may take place when either there is loss of inhibitors or with the appearance of calcification promoters, eg, crystal nucleators. As the detailed mechanisms of calcification remain poorly understood, the exact cause of calcification in individual patients is unlikely to be determined (10). The dystrophic mineral deposition which occurs in atherosclerosis may bear on mechanisms of calcification in other settings. In atherosclerotic plaque, calcification may involve the participation of

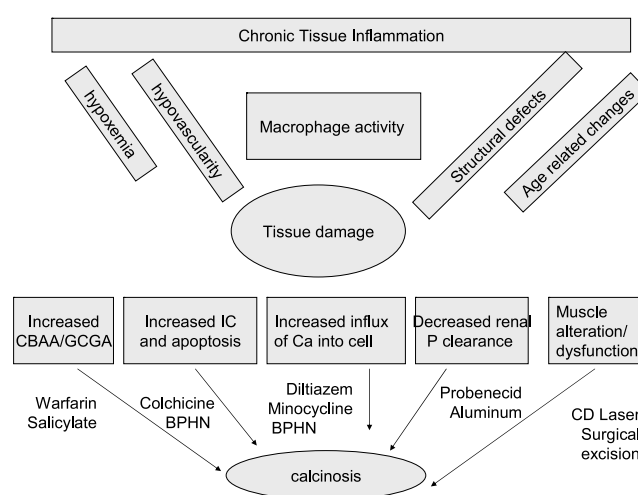


Figure 3 Proposed pathophysiological scheme of development and treatment of calcinosis.

arterial osteoblasts and osteoclasts (11). Further, as atherosclerosis is a consequence of chronic vascular inflammation, the mechanism of dystrophic calcification in arterial plaque may be underlying inflammation. Increased levels of the calcium binding amino acid (CBAA) and gamma-carboxyglutamic acid (GCGA) have been measured in patients with calcinosis (12–15). Additionally, the presence of macrophages, interleukin (IL)-6, IL-1 β , and tumor necrosis factor (TNF)- α in the “milk of calcium deposits,” together with detectable levels of IL-1 β in the serum (16), have suggested that activated macrophages play an important role in the development of calcinosis in juvenile dermatomyositis (JDM). Kim (17), on the other hand, concluded that apoptosis most likely underlies the mechanism of both physiological and pathological calcification.

Clinical Features of Calcinosis in Rheumatic Diseases

General Features

Calcinosis may be limited, involving a relatively localized area, with small deposits in the skin and subcutaneous tissues, especially over the extensor aspects of the joints and fingertips. Or it may be widespread, not only in the skin and subcutaneous tissues, but also deeper in periarticular regions and areas of repeated trauma (18–20). The accumulation of calcinotic material may form small- or medium-sized hard nodules that, secondarily, induce muscle atrophy and contractures (19). In some cases calcinosis evokes recurrent episodes of local inflammation that mimic infection, and the crystalline material of calcific lesions may ulcerate the skin.

Systemic Sclerosis (SSc)

Subcutaneous calcinosis, composed of calcium hydroxyapatite (HA) deposits at sites of recurrent microtrauma such as the forearms, elbows, or fingers, occurs in many individuals

with SSc but is more prominent in those with limited scleroderma and especially in those patients with anticentromere antibody. Robertson and coworkers (21) reported that calcinosis occurs in about 25% of patients with scleroderma, usually those with limited cutaneous SSc. Pseudoxanthoma elasticum-like calcification (22) and dystrophic calcinosis secondary to localized linear scleroderma (23) also have also been described. Calcinosis may be superficial, ulcerating the skin and thereby leading to secondary infection. Recently, a tumoral calcinosis-like lesion about the shoulder was reported (24). More often, the deposits remain simply as bothersome subcutaneous lumps which may rarely cause recurrent local inflammation due to the release of HA crystals into the surrounding tissue (20). Painful calcification of the digits may be associated with ischemia and nerve pain in SSc (25).

Polymyositis and DM

Soft-tissue calcification occurs most commonly in chronic DM, especially with onset in childhood, being uncommon in adult-onset disease (26–30). In their classical study, Bowyer and coworkers (28) reported calcinosis in about 40% of cases of JDM, correlating with skin disease severity, vasculopathy, and delay in initiating therapy to control muscle and skin inflammation. According to a recent summary (27), approximately 30 to 70% of children with JDM develop calcinosis, typically late in the disease course and quite disabling. Myositis may be well controlled when calcinosis first appears, but the affected patients most often have had chronic, active disease previously or a delay in the initiation of treatment (27). The calcium deposits may be intracutaneous, subcutaneous, fascial, or intramuscular, with predilection for sites of repeated microtrauma—such as of elbows, knees, flexor surfaces, and buttocks. Troubling complications include cutaneous ulceration with drainage of calcareous material and secondary infection and joint contractures that interfere with physical function (27).

Calcinosis in JDM has several distinct forms (29): small scattered superficial plaques or nodules, usually on the extremities, with no interference with function; deep tumoral muscular deposits which may interfere with joint motion when they appear close to joints, occasionally ulcerating or extruding calcific material through the skin; diffuse deposits along myofascial planes that may limit joint motion and are often painful; and mixed forms of the above 3 types. Generalized superficial calcification with a lacy reticular radiographic pattern forming an extensive exoskeleton also has been described (30) in patients with severe generalized erythroderma. This latter form does not appear to be related to delay in diagnosis and treatment in contrast to other manifestations of calcinosis in JDM.

SLE

Calcific involvement of the musculoskeletal system has been noted commonly, when looked for, in some SLE patient series (31–33). It may involve the joints and worsen myopathy (31). Calcification in SLE may be periarticular (32) with a clinical picture similar to calcinosis in SSc or DM as described

above—subcutaneous calcifications with ulcerations, local infections, and contractures. Okada and coworkers (33) reported an unusually high prevalence of ectopic calcification in SLE in 40% of patients—7% in peripheral arteries, 33% in periarticular areas, and 17% in other soft tissues (7% in multiple locations). The coincidental report of arterial calcification in this patient survey highlights premature coronary artery disease, with plaque calcification as an increasingly major cause of morbidity and mortality in patients with SLE (34). Cerebral calcification also has been described in an elderly lupus patient (35). The relationship of vascular and CNS calcification to periarticular and soft-tissue calcium deposits has not been well addressed.

Treatment of Calcinosis

No pharmacological treatment is generally accepted as standard treatment to prevent or reduce calcinosis. Calcinosis treatment suffers from a notable lack of controlled clinical trials. Warfarin, colchicine, probenecid, bisphosphonates, and diltiazem have been tried with variable success (36). Surgical extirpation can be of benefit for larger lesions (36) and smaller superficial lesions may be effectively treated with carbon dioxide (CO₂) laser therapy (37). Minocycline (21), aluminum hydroxide (38), and salicylate (15) therapy to decrease GCGA excretion represent additional treatment options. Aggressive management of JDM directed at achieving rapid and complete control of muscle inflammation may improve outcome and decrease the incidence of calcinosis (39) (Table 1).

Warfarin

Increased levels of CBAA and GCGA have been measured in patients with calcinosis. The enzyme which effects gamma carboxylation of glutamic acid is warfarin-sensitive (12,13). In a pilot study, 4 patients with calcinosis and DM or SSc were treated with 1 mg per day of warfarin for 18 months in a nonblinded fashion. In 2 of these, both decreased GCGA urinary concentration and decreased extraskeletal isotope uptake on technetium 99m-diphosphonate whole-body nuclear scanning were subsequently demonstrated (12). In a double-blind placebo-controlled study which followed, two-thirds of the patients receiving 1 mg per day of warfarin had a decrease in extraskeletal nuclear tracer uptake after 18 months, compared with none of the 4 patients receiving placebo. No patient had a change in clinical assessment, bleeding complication, or change from baseline normal prothrombin time (PT). Thus the low-dose warfarin regimen appeared to have no demonstrable adverse effect, with a suggested beneficial effect on the laboratory progression of calcinosis in the study patients (12).

Lassoued and coworkers (40), on the other hand, found no improvement in 6 patients with long-standing diffuse calcinosis treated with warfarin for 1 year. In a case reported subsequently, the use of low doses of warfarin to treat calcinosis in a patient with SSc-CREST syndrome was described (41). After beginning warfarin, a calcium-containing sub-

Table 1 Proposed Treatments for Calcinosis

Treatment and Doses	Possible Mechanisms	Side Effects
Warfarin 1 mg/day ^(12,13,40-42)	Decreases CBAA, GCGA excretion, and vitamin K levels	None
Colchicine 1 mg/day ^(10,46)	Antiinflammatory effect	Abdominal pain Diarrhea
Probenecid 250-2000 mg/day ^(23,47-50)	Increases renal phosphate clearance	Rash Diarrhea Nephrolithiasis
Disodium etidronate 20 mg/kg/day ^(14,51-53)	Decreases progression of the calcification process	Peptic disease Bone pain Headache
Alendronate 10 mg/day ⁽¹⁴⁾	Decreases the calcification process	Peptic disease Bone pain Headache
Diltiazem 240 mg/day ⁽⁵⁵⁻⁶¹⁾	Inhibition of calcium influx into cells	Edema Hypotension
Surgical excision ⁽⁶²⁾	Mechanical improvement	Surgical wound complications
Carbon dioxide laser ^(37,63)	Mechanical improvement	Infection
Aluminum hydroxide 1.68-2.24 g/day ^(38,64-68)	Possible reduction in serum phosphate	No adverse effects reported, contraindicated in renal failure
Minocycline 50-100 mg/day ⁽²¹⁾	Inhibition of matrix metalloproteinases, Ca binding, antibiotic effects	Darkening of the calcinosis to a blue/black color
Salicylates 80 mg/kg/day ⁽¹⁵⁾	Decreased GCGA excretion	Abdominal pain Peptic ulcer disease Salicylism
Intralesional adrenal steroids ⁽⁶⁹⁾	Mechanical improvement	Infection
Anti-TNF 3-5 mg/kg ^(70,71)	Antiinflammatory effect?	Allergic reaction Infection

stance no longer discharged from a fingertip ulcer and sequential radiographs of the hand showed that calcinosis had improved. There was no tendency to bleed nor PT abnormality. In another case, vitamin K levels were initially abnormally high in a patient with DM, decreased after starting warfarin therapy, and remained within the normal range. Since vitamin K is thought to play an important role in the calcium-binding process in bone, warfarin may reduce subcutaneous calcification through its effect on the vitamin K cycle (42). Most recently, Cukierman and coworkers (43) reported that 2 of 3 patients with SSC responded well to low-dose warfarin therapy.

Colchicine

Inflammation provoked by calcific deposits is responsible for a significant amount of the morbidity associated with calcinosis. Colchicine inhibits microtubule polymerization by binding microtubule protein subunits and preventing their aggregation, thus setting the stage for disruption of such membrane-dependent functions as leukocyte chemotaxis and phagocytosis (10). Clinically, colchicine is useful in preventing inflammation secondary to calcium deposits in pseudogout and calcific bursitis (44,45). In a case of ulcerated cutaneous calcinosis associated with linear scleroderma, healing of the ulcerations took place after 4 months of treatment with colchicine 1 mg per day (46).

Probenecid

Probenecid, a sulfonamide derivative, is a uricosuric agent that inhibits the reabsorption of uric acid in the proximal tubule (26). In JDM, probenecid was felt to be effective in reducing calcification by increasing renal phosphate clearance (26) and led to a dramatic decrease in subcutaneous and intramuscular calcinosis (47). Dent and Stamp (48) reported that probenecid was effective in a patient with progressive calcinosis associated with connective tissue disease. Ansell (49) noted an improvement in 3 of 5 patients with extensive calcinosis of JDM treated with probenecid 2 g/day. More recently, Eddy and coworkers (50) described a case of severe calcinosis of JDM treated successfully with probenecid 250 to 1500 mg/day. A thorough biochemical study before treatment revealed an elevated serum phosphorus level and increased renal tubular reabsorption of phosphate. The calcification in JDM might, at times, be related to altered phosphorous metabolism, in addition to the inflammatory damage induced by the underlying disease (26).

Bisphosphonates

Bisphosphonates reduce calcium turnover, a source for calcium deposition, and have a potent effect on macrophage cell lineage, causing selective destruction of macrophages and inhibiting macrophage proinflammatory cytokine produc-

tion (16). This form of therapy seems to arrest and partially reverse the progression of the calcifying process. A patient with scleroderma and extensive disabling calcinosis was treated with disodium etidronate (51). Some deep calcific deposits dissipated and were partially resorbed, while some small superficial deposits diminished. Clinically, pain was reduced, recurrent abscess formation ceased, and joint mobility improved (51). In contrast, another study reported failure of etidronate therapy (52) with the untoward appearance of a gastric ulcer as a potential complication (53). More recently, alendronate was administered to a pediatric patient with JDM and calcinosis with dramatic response in inflammation, ectopic calcification, and improved range of movements (16). The different mechanism of action of the aminobisphosphonates from that of the older bisphosphonates (54) on enzyme inhibition and apoptosis may contribute to greater efficacy in this indication.

Diltiazem

Diltiazem has been used to treat calcinosis in active SSc. In one case, calcinosis, which remained static for several years, regressed when diltiazem was used to treat hypertension. This effect could not be explained by altered disease activity or renal function but was thought to be due to inhibition of calcium influx into cells (55). In this regard, diltiazem may exert its benefit by influencing intracellular calcium levels in macrophages.

Farah and coworkers described a patient with the scleroderma CREST subset who was treated with diltiazem 240 mg/day for 5 years with arrest of the clinical progression of calcinosis and a parallel decrease in the uptake of bone scan radionuclide in soft-tissue foci (56). On the other hand, another study did not indicate that diltiazem was effective in calcinosis associated with SSc (57). Palmieri and coworkers (58) treated 4 patients with idiopathic or CREST-related calcinosis with diltiazem 240 to 480 mg/day for 1 to 12 years. A fifth patient, who did not tolerate diltiazem, received verapamil 120 mg/day. Prolonged treatment with diltiazem, but not verapamil, was accompanied by reduced calcinosis. Oliveri and coworkers (59) reported an 8-year-old girl with JDM treated with diltiazem, 5 mg/kg/day, who had dramatic regression of calcinosis after 21 months of therapy. More recently, Vinen and coworkers (60) described a successful case of diltiazem treatment of calcinosis in adult DM. Further, Morgan and coworkers (61) reported a response to diltiazem and chloroquine in calcifying lupus panniculitis.

Surgery and CO₂ Laser Treatments

Large calcium deposits may be the source of considerable morbidity secondary to tumor tenderness and functional disability. For palliation, complete surgical excision of larger lesions may be the treatment of choice (62), although calcification may recur locally on a smaller scale. Smaller superficial lesions, on the other hand, can be effectively treated with CO₂ laser (37). The CO₂ laser, developed in the 1960s, provides both surgical precision and a bloodless field, offering a useful alternative to scalpel surgery in certain situations.

As palliative treatment for cutaneous calcinosis, this modality, though tedious, was both effective and well tolerated (63). One study evaluated this treatment in 6 patients with limited SSc. A total of 21 areas of symptomatic digital calcification of the fingers was treated. Complete resolution of symptoms occurred in 12; moderate response with partial improvement was seen in 5; little improvement was observed in 2; and recurrence of calcinosis was found in 2. Postoperative infections complicated the course in 2 patients, with complete resolution with the use of topical and oral antibiotics (37). Chamberlain and coworkers (63) utilized CO₂ laser vaporization to treat digital CREST-related calcinosis in a single patient over a 5-year period with significant improvement in symptoms. The treated digits took an average of 6 weeks to heal. The ulcers did not recur on the treated digits for more than 3 years.

Aluminum Hydroxide (AH)

In several reported cases DM-associated calcinosis cutis responded well to AH therapy (64-66) with no adverse effects. The mechanism underlying this putative improvement is not understood but may relate to phosphorus binding by aluminum salts. Park and coworkers (67) treated long-standing SLE patients with multiple subcutaneous calcifications with AH with a resultant moderate decrease in size and softening in consistency, but without complete resolution. Nakagawa and coworkers (38) described almost complete clearing of calcinosis in a JDM patient after 8 months of AH therapy. Hudson and coworkers (68) described a good response in SSc patients. Caution should be exercised in using AH in SLE patients with renal insufficiency as aluminum may accumulate and cause osteomalacia, myopathy, or dementia.

Minocycline

Low-dose minocycline may be effective in controlling calcinosis in SSc (21) and appears to be generally well tolerated. Minocycline may act through inhibiting matrix metalloproteinases, as well as by its antiinflammatory effect. The drug's calcium binding properties and antibacterial action may also play a role. In this recent study, improvement occurred in all 9 treated patients with the earliest response after 1 month, with mean time to resolution of 4.8 ± 3.8 months (21).

Salicylate Therapy

Proteins containing GCGA are found in tissues involved with subcutaneous calcinosis, with a 3-fold increase in GCGA excretion noted in such patients with JDM. Decreased excretion of this amino acid has been demonstrated with salicylate therapy (15).

Intralesional Injection of Corticosteroids

Intralesional injection of corticosteroids may be effective in palliation and control of calcinosis in SSc with reduction of secondary inflammation (69). As reported, this treatment appears to be well tolerated.

New Possible Treatments of Calcinosis

Many new small molecule and biological agents are undergoing evaluation in patients with DM: cyclosporine, intravenous immunoglobulin, and TNF-alpha inhibitors have been reported to be of benefit in resistant disease and improved calcinosis (70,71). The efficacy of tacrolimus, mycophenolate mofetil, and leflunomide therapy needs evaluation in prospective studies to determine if these agents are of value in idiopathic inflammatory myositis with secondary calcinosis (71).

Discussion

Calcinosis, soft-tissue calcification which occurs in the presence of normal metabolism in damaged or devitalized tissues, is widespread in connective tissue diseases with a prevalence of 17% in SLE, about 25% in scleroderma, and 30 to 70% in DM, including JDM. Although calcinosis is the source of significant pain and disability in these patients, the literature reveals a paucity of studies of its treatment, many reports being extended case descriptions. The lack of a unified classification of soft-tissue calcification, and the place of calcinosis therein, complicates reading of the literature and obfuscates systematic study of the subject. No pharmacological treatment prevents or eliminates calcinosis. Thus, no clear recommendations or approach to this problem have emerged from this review. Warfarin, colchicine, bisphosphonates, probenecid, and diltiazem have all been used with variable success and may be tried singly or in combination in individual cases, depending on the clinical circumstances. Surgical extirpation is of benefit in troublesome larger lesions, while smaller superficial lesions may be effectively treated with CO₂ laser as adjunctive therapy. This report draws attention to the problem, focuses on treatment options (Table 1), and encourages further study with larger, comparative, or controlled trials.

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